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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/074,169	02/12/2002	Carl T. Wittwer	7475-70049	5884

49437 7590 01/26/2006

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ART UNIT	**PAPER NUMBER**
1637	

DATE MAILED: 01/26/2006

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/074,169
Filing Date: February 12, 2002
Appellant(s): WITTWER, CARL T.

Rebecca L. Ball
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed December 23, 2005 appealing from the Office action mailed May 23, 2005.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

No amendment after final has been filed.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

6,387,621	Wittwer	5-2002
EP 1059523 A2	Wittwer	12-2000

Herrman et al. "Rapid B-globin genotyping by multiplexing probe melting temperature and color". Clinical Chemistry, Vol. 46, No. 3 (2000), pp. 425-428.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Double Patenting

Claims 1 and 3-10 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-24 of U.S. Patent No. 6,387,621 in view of Herrmann et al (Clin. Chem. (2000) 46(3):425-428).

Claims 1-2 of U.S. Patent No. 6,387,621 teach a method for determining the presence of a nucleic acid comprising the

steps of

(a) providing a fluorescent entity capable of indicating the presence of the nucleic acid and capable of providing a signal related to the quantity of the

nucleic acid,

(b) amplifying the nucleic acid through a plurality of amplification cycles in the presence of the fluorescent entity,

(c) measuring fluorescence intensity of the fluorescent entity at each of the plurality of amplification cycles to produce a fluorescent value for each cycle related to the quantity of the nucleic acid present at each cycle,

(d) generating a fluorescence-verses-amplification-cycle plot wherein the fluorescent values are recorded for each amplification cycle,

(e) calculating slopes of segments of the fluorescence-verses-amplification-cycle plot using a plurality of the fluorescent values, using the segment slopes of the fluorescence-verses-amplification-cycle plot to establish a baseline fluorescence region by generating a slope value for each of a plurality of the amplification cycles, and establishing the baseline fluorescence region comprising an interval of cycles that includes the amplification cycle with the slope value having an absolute value closest to zero, and ascertaining whether the fluorescence value during a selected amplification cycle is outside the baseline fluorescence region.

With regard to claim 3, Claims 1-24 of U.S. Patent No. 6,387,621 do not require an internal standard.

With regard to claim 10, Claim 13 of U.S. Patent No. 6,387,621 teaches the automated method.

Claims 1-24 of U.S. Patent No. 6,387,621 do not teach confirmining the results by a melting temperature analysis.

Herrman teaches performing a PCR reaction followed by confirming the target using a melting temperature analysis (see page 425, column 2).

With regard to claim 4, Hermann teaches obtaining a melting profile (see figure 1), determining the minima or maxima based upon the dF/dT derivative melting curves (see figure 1 and page 427, column 1) and comparing the Tm with the known Tm (see figure 1 and page 427, column 1).

With regard to claims 5-7, Hermann teaches performing the method subsequent to amplification, but MPEP 2144.04 notes "selection of any order of performing process steps is prima facie obvious in the absence of new or unexpected results" In this case, with regard to claims 5 and 6, the monitoring step is identical to that performed after amplification and would have been expected to function in the same way during amplification, with the variation simply being an increasing amount of target available to the probe as amplification proceeds, so the order of the steps is prima facie obvious.

With regard to claims 8 and 9, Hermann teaches monitoring fluorescence at 0.1 C/s increments (see page 427, column 1) which encompasses monitoring at longer increments.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the confirmatory melting temperature analysis method of Herrmann with the PCR method of Claims 1-24 of U.S. Patent No. 6,387,621 since Hermann states "The ability to multiplex PCR analysis by color and Tm has many uses in addition to multiplex genotyping. For example, internal amplification controls are often needed for infectious disease and translocation testing to verify that amplifiable DNA or cDNA is present even if the target amplification is negative. Another common need is for multiplexing a competitor as an internal standard for PCR quantification (see page 428, column 1)." Thus, an ordinary practitioner would have been motivated to confirm the PCR analysis with a melting point analysis in order to perform a variety of checks, including multiplex genotyping, internal controls and internal competitors as standards. Further, it would have been prima facie obvious to

combine Hermann with any analytical PCR method to improve the specificity and validity of the method for the reasons cited from the Hermann paper. This additional verification solves the problem, recognized by U.S. Patent No. 6,387,621 that " accurately discriminating between positive and negative samples is not easy in practice (see column 6, lines 15-16)" The specification continues, noting "Automatic identification of the background is surprisingly difficult. (see column 6, lines 48-49)." Hermann provides one solution for this problem by providing a means to accurately discriminate between positive and negative PCR samples such as those used by U.S. Patent No. 6,387,621 which would further support the determination made by the analytical method of U.S. patent 6,387,621.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and

> the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1 and 3-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wittwer et al (EP 1059523 A2) in view of Herrmann et al (Clin. Chem. (2000) 46(3):425-428).

Wittwer teaches a method, which uses automated processes such as a fluorometer and computer for plotting (see column 6, paragraph 0022), for determining the presence of a nucleic acid (see abstract) comprising the steps of:

a) providing a fluorescent entity, SYBR Green dye, which is capable of providing a signal indicating the presence and amount of a nucleic acid (see column 5, paragraph 0019),

b) amplifying the nucleic acid through a plurality of amplification cycles in the presence of the fluorescent entity, SYBR green acid (see column 5, paragraph 0019),

c) measuring the fluorescence of the fluorescent entity during each of the plurality of amplification cycles acid (see column 5, paragraph 0019),

d) generating a plot wherein the fluorescent values are recorded for each amplification cycle (see figure 5, for example

e) performing a confidence band analysis by calculating slopes of segments of the plot using a plurality of the fluorescent values, using the segment slopes of the plot to establish a baseline nuorescence region by generating a slope value for each of a plurality of the amplification cycles, and establishing the baseline florescence region comprising an interval of cycles that includes the amplification cycle with the slope value having an absolute value closest to zero, outputting a positive result if the fluorescence value of a selected amplification cycle is outside the baseline fluorescence region (see figure 5, columns 8-10 and claims 2-14).

With regard to claim 3, Wittwer teaches that the baseline is established without the use of an internal standard (see columns 9-10).

Wittwer does not teach confirming the results by a melting temperature analysis.

Herrman teaches performing a PCR reaction followed by confirming the target using a melting temperature analysis (see page 425, column 2).

With regard to claim 4, Hermann teaches obtaining a melting profile (see figure 1), determining the minima or maxima based upon the dF/dT derivative melting curves (see figure 1 and page 427, column 1) and comparing the Tm with the known Tm (see figure 1 and page 427, column 1).

With regard to claims 5-7, Hermann teaches performing the method subsequent to amplification, but MPEP 2144.04 notes "selection of any order of performing process steps is prima facie obvious in the absence of new or unexpected results" In this case,

with regard to claims 5 and 6, the monitoring step is identical to that performed after amplification and would have been expected to function in the same way during amplification, with the variation simply being an increasing amount of target available to the probe as amplification proceeds, so the order of the steps is prima facie obvious.

With regard to claims 8 and 9, Hermann teaches monitoring fluorescence at 0.1 C/s increments (see page 427, column 1) which encompasses monitoring at longer increments.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the confirmatory melting temperature analysis method of Herrmann with the PCR method of Wittwer since Hermann states "The ability to multiplex PCR analysis by color and Tm has many uses in addition to multiplex genotyping. For example, internal amplification controls are often needed for infectious disease and translocation testing to verify that amplifiable DNA or cDNA is present even if the target amplification is negative. Another common need is for multiplexing a competitor as an internal standard for PCR quantification (see page 428, column 1)." Thus, an ordinary practitioner would have been motivated to confirm the PCR analysis of Wittwer with a melting point analysis of Hermann in order to perform a variety of checks, including multiplex genotyping, internal controls and internal competitors as standards. Further, it would have been prima facie obvious to combine Hermann with any analytical PCR method to improve the specificity and validity of the method for the reasons cited from the Hermann paper. This additional verification solves the problem, recognized by Wittwer that " accurately discriminating between positive and negative

samples is not easy in practice (see column 7, lines 23-24)" The specification continues, noting "Automatic identification of the background is surprisingly difficult. (see column 7, paragraph 0027)." Hermann provides one solution for this problem by providing a means to accurately discriminate between positive and negative PCR samples such as those used by Wittwer which would further support the determination made by the analytical method of Wittwer.

(10) Response to Argument

Introduction

In order to understand the issues in this application, the underlying technology will be briefly discussed. The claimed invention is drawn to methods of detecting nucleic acids during an amplification reaction. The current application teaches methods of measuring the intensity of fluorescent labels during a nucleic acid amplification reaction to determine how much and whether the nucleic acid is present. Both the prior art method of Wittwer (whether in the double patenting rejection or in the 103 rejection) and the current claims share the same steps of providing the fluorescent entity, amplifying that entity, measuring fluorescence intensity, generating plots of the fluorescent values, performing confidence band analyses and using the slopes of the segments of the plot to make the confidence call.

In fact, the claims of U.S. Patent 6,387,621 (and the teaching in EP 1059523 A2) effectively differ from the current claims only by the inclusion of one step, which is "if the call is positive, confirming the positive call by a melting temperature analysis".

Prima facie case

The prima facie case of obviousness under 35 U.S.C. 103 is based upon two references, Wittwer (EP 1059523 A2) and Herrmann et al (Clin. Chem. (2000) 46(3):425-428). Similarly, the obviousness type double patenting rejection is based upon the claims of U.S. Patent 6,387,621 in view of Herrmann et al (Clin. Chem. (2000) 46(3):425-428). Wittwer, whether in the EP or in the claims of the U.S. Patent, teaches each and every limitation of the invention except for the inclusion of a confirmation step by melting temperature analysis.

Herrman teaches the combination of fluorescence detection and melting temperature analysis, where the melting temperature analysis is used to verify the presence of the amplified sequence of interest.

The Appellant does not dispute that the two references teach every element of the invention. Appellant argues that there is no motivation to combine the teaching of Herrmann with Wittwer (EP 1059523 A2) in the 103 rejection or with the claims of U.S. Patent 6,387,621 in the double patenting rejection.

Motivation

Direct Motivation

In addressing the motivation issue, the combination of the claims of U.S. Patent No. 6,387,621 and Hermann is based upon a simple premise, that Hermann's teaching that temperature melting can be confirmatory of successful or unsuccessful PCR methods is desirably combined with the claims of U.S. Patent No. 6,387,621 to

determine whether that method is successful. Hermann expressly teaches that the temperature melting method can be used as a confirmatory control, as already quoted in the rejection above "The ability to multiplex PCR analysis by color and Tm has many uses in addition to multiplex genotyping. For example, internal amplification controls are often needed for infectious disease and translocation testing to verify that amplifiable DNA or cDNA is present even if the target amplification is negative. Another common need is for multiplexing a competitor as an internal standard for PCR quantification (see page 428, column 1)."

While Appellant argues that express motivation to combine the steps of generating a positive call by confidence band analysis and confirming with melting temperature analysis is absent, there is some suggestive motivation to combine fluorescence analysis with the melting temperature analysis as expressly stated by Herrman. Herrman teaches that "By multiplexing the probe T_mS and only two colors, we were similarly able to genotype three different point mutations. An additional advantage of using hybridization probes is that unexpected sequence alterations can be detected (see page 428, column 1)." Here Herrman expressly teaches that the melting temperature analysis, T_mS, is combined (multiplexed) with the analysis of two colors to permit multiplexing. Herrman teaches multiplexing of the fluorescence detection that forms the base of the Wittwer method with confirmation of the fluorescence call by melting temperature analysis. The ability to genotype multiple different mutations along with the ability to detect unexpected alterations both provide motivation to confirm the fluorescence analysis with the melting temperature analysis of Herrrman.

With regard to the rejection with Wittwer (EP 1059523 A2), Wittwer expressly teaches "Perhaps the most basic analysis of real time PCR data is a judgement of whether a targeted nucleic acid is present. If the nucleic acid is present, further quantification and genotyping may take place (see page 6, lines 55-59)." This provides nearly direct motivation to perform additional steps such as the melting temperature analysis of Herrman (which will function to genotype a sample) following the real time PCR analysis.

Consequently, given the teaching of Wittwer to perform further genotyping after real time PCR provides the yes/no answer and the teaching of Herrman to genotype using melting temperature analysis, there is significant evidence to support a finding of direct motivation to combine the teachings of Wittwer with those of Herrman.

Nature of the Problem to be Solved motivation

Further, In Ruiz v. A.B. Chance Company, (Fed. Cir. 2004), heard on an appeal after remand, the Federal Circuit noted " While this court indeed warns against employing hindsight, its counsel is just that – a warning. That warning does not provide a rule of law that an express, written motivation to combine must appear in prior art references before a finding of obviousness. Stated differently, this court has consistently stated that a court or examiner may find a motivation to combine prior art references in the nature of the problem to be solved. " In the current case, the motivation derives from both bases cited by the Federal Circuit. There is strong direct motivation from Hermann to use the melting temperature method to control for variation

and to multiplex, particularly in combination with the allelic analysis method of claim 11 of U.S. Patent 6,387,621.

Second, the nature of the recognized problem in U.S. Patent No. 6,387,621 lends itself to solution by combination with the Hermann reference. The additional verification provided by using the Herrman melting temperature method solves a problem, recognized by U.S. Patent No. 6,387,621 that "accurately discriminating between positive and negative samples is not easy in practice (see column 6, lines 15-16)" The specification continues, noting "Automatic identification of the background is surprisingly difficult. (see column 6, lines 48-49)." Hermann provides one solution for this problem by providing the melting temperature method, which Herrman demonstrates is a method that accurately discriminates between positive and negative PCR samples such as those used by U.S. Patent No. 6,387,621.

Appellant argues that the problem presented in U.S. Patent No. 6,387,621 is solved by the confidence band analysis alone, and that therefore this problem does not provide motivation to combine the method of Herrman. This is not correct, since U.S. Patent No. 6,387,621 expressly recognizes a number of problems, including "This algorithm should work well in most cases. However, with the high copy fluorescence curve type (FIG. 3D), the shallowest slope might be found at early cycles (resulting in a correct positive call) or at late cycles (resulting in an incorrect negative call) (see column 7, lines 5-8)." While the patent addresses these problems, the ordinary practitioner would recognize that additional confirmatory steps would render the determination more precise and more accurate.

In fact, it is a standard concept in molecular biology and in science in general to confirm results using different types of controls. This is evidenced by Herrman, who teaches the use of a no template control (see figure 1, panel b legend). Herrman also teaches multiplexing color detection and melting temperature detection (see page 428, column 1, for example). An ordinary practitioner, taught by the totality of the prior art to perform controls and specifically taught by Herrman to measure PCR by both color detection and melting temperature, would have been motivated to improve the accuracy of the color detection by using the confidence banding method of Wittwer and retain the melting temperature method as a control, since Herrman expressly teaches multiplexing the method and since the ordinary practitioner is well aware that controls improve the accuracy of results.

Appellant argues that the problems listed in U.S. Patent No. 6,387,621 were taken out of context since the problems were also addressed in the patent. As a legal doctrine, the argument that the fact that the patent provides a solution to a problem abolishes any later motivation to improve on the solution to that problem is illogical. Simply because the patent provides some solutions for a problem does not denigrate the motivation provided by the problem to make further improvements and further contributions. This is most evident in the long history of mousetraps, where the nature of the problem to be solved, catching a mouse, while addressed by many patents through the years, is still the subject of active applications and recent patents. Clearly there is motivation in the art to improve the methods even though some solutions have been presented. The same logic applies in the current case, and the recognition that

accurate discrimination of postives and negatives can be improved by applying the Herrman method to the current claims provides substantial motivation to combine either the claims of U.S. Patent No. 6,387,621 or the Wittwer EP document with the teachings of Herrman.

Appellant then argues that Herrman solves a different problem, which is not discriminating between positive and negative calls but rather is involved in differentiating multiple DNAs in a sample. In fact, Herrman does both. In analyzing genotypes using the method of Herrman, the method necessarily determines both whether the nucleic acid genotype is present or not, and secondarily which genotype is present, if any are. This is clearly demosntrated by the presence of the "no template control" in figure 1. Herrman shows that the "no template control" has a line which does not extend above baseline while the samples with template show specific –dF/dT derivative melting curves. So contrary to Appellant's argument, Herrman does differentiate between a positive and negative call and will provide this information, along with the genotype information that also will provide specific calls regarding the presence of a first homozygous allele, a second homozygous allele or a heterozygote that has one copy of both the first and second alleles (see figure 1 of Herrman).

Claims 3, 5, 6 and 9 rejection

Appellant separately argues that claims 3, 5, 6 and 9 should be allowed because there is no suggestion of establishing the baseline region without the use of an internal standard in the patent claims or Herrman (and presumably in the Wittwer EP document

as well). This is simply not correct in fact. Claim 3 of U.S. Patent 6,387,621 states "The method of claim 1 wherein the amplification cycle with the slope value having the absolute value closest to zero comprises a central cycle of the interval of cycles used to establish the baseline fluorescence region." This is a clear teaching to establish the baseline region without any requirement for an internal standard. This claim expressly teaches tha the baseline region is established based upon a particular amplification cycle and not based upon any internal standard. Thus, claim 3 of U.S Patent 6,387,621 expressly teaches this limitation. Similarly, Wittwer also teaches the same concept (see claims 2 and 4 and column 10 of the Wittwer EP document).

With regard to the elements in claims 5, 6 and 9, Herrman expressly teaches these elements as discussed in the rejections. Herrman teaches performing a PCR reaction followed by confirming the target using a melting temperature analysis (see page 425, column 2). With regard to claims 5 and 6, Hermann teaches performing the method subsequent to amplification. In this case, with regard to claims 5 and 6, the monitoring step is identical to that performed after amplification and would have been expected to function in the same way during amplification, with the variation simply being an increasing amount of target available to the probe as amplification proceeds, so the order of the steps is prima facie obvious. With regard to claim 9, Hermann teaches monitoring fluorescence at 0.1 C/s increments (see page 427, column 1) which encompasses monitoring at longer increments.

Reasonable expectation of success

Appellant does not argue that there is a lack of any reasonable expectation of success.

Secondary Considerations

Appellant argues no secondary considerations.

Conclusion

Therefore, since the claims of U.S. Patent No. 6,387,621 and Herrman references (as well as the Wittwer and Herrman references in the 103 rejection) teach each and every limitation of the claimed invention and since Herrman solves the identification problem of Wittwer as well as permitting the genotyping expressly suggested by Wittwer with a reasonable expectation of success, the 35 U.S.C. 103(a) and double patenting rejections should be sustained.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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